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Tidal volumes and outcome of extubation in mechanically ventilated premature infants

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Short title: Extubation tidal volumes in premature infants

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ABSTRACT

Aims: To compare the pre-extubation tidal volumes (V_T) in ventilated, prematurely-born infants who were successfully extubated compared to those who failed extubation and determine whether V_T predicted successful extubation.

Methods: A two-centre prospective cohort study of ventilated infants born<32 weeks of gestational age (GA) was undertaken between February and September 2018. Expiratory V_T was recorded immediately before extubation. Extubation was considered successful if the infants were not reintubated within 72 hours.

Results: Fifty-six (29 male) infants with a median (interquartile range, IQR) GA of 26 (25–29) weeks were studied. The infants that were successfully extubated (*N*=36) had a higher GA [27(25–30) weeks] and V_T [7.2(4.8–9.5) ml] compared to the GA [25(24–26) weeks] and V_T [4.3(4.0–5.5)ml] of the infants that failed extubation (p=0.002 and p=0.001 respectively). Following multivariate regression, V_T was associated with extubation success (adjusted p=0.022), but GA was not (adjusted p=0.167). A V_T>4.5 ml predicted successful extubation with 82% sensitivity and 58% specificity (AUC=0.786).

Conclusion: Infants who were successfully extubated had significantly higher tidal volumes compared to those who failed extubation. We speculate that a low V_T prior to extubation might cause atelectasis and lead to extubation failure.

Key words: extubation, tidal volume, prematurely-born infants

KEY NOTES

- In the era of volume-targeted ventilation, it is not known whether the targeted volumes influence the outcome of extubation.
- We studied 56 prematurely-born ventilated infants at two large teaching hospitals in London and measured their tidal volumes before extubation.
- Successful extubation was associated with ventilation with higher tidal volumes compared to failed efforts and tidal volume predicted successful extubation with moderate sensitivity and specificity.

INTRODUCTION

Volume-targeted ventilation (VTV) has become the mainstream mode of mechanical ventilation in prematurely born infants due to the significant benefits of VTV such as the decrease in death or bronchopulmonary dysplasia (BPD), incidence of intraventricular haemorrhage (IVH) and duration of mechanical ventilation (1, 2). The actual targeted value of the tidal volume (V_T) varies in different diseases due to the underlying pathophysiological processes (3) with suggested targeted tidal volumes ranging from 4 (4) to as high as 12 ml/kg of body weight (5). This wide range of values might be explained by the observation that alveolar dead space increases with a longer duration of mechanical ventilation and weight-adjusted anatomical dead space increases with lower gestation and body weight (6, 7). In evolving BPD altered respiratory mechanics, such as increased resistance, necessitate the provision of “supra-physiologically” high tidal volumes (5, 8). While some experts have recommended actual values for the targeted V_T (3, 9, 10), very few studies have investigated weaning strategies and targeted V_T at extubation.

Accurate assessment of readiness for extubation is clinically desirable as prolonged mechanical ventilation is injurious and too early extubation increases the risk of respiratory failure and reintubation (11). Predicting the outcome of extubation is a complex process that depends on a number of interrelated parameters such as the adequacy of the neural signal, the integrity of the neuromuscular synapse, the functional capacity of the respiratory muscles and the primary lung pathology (12). Various univariate or multivariate models have been proposed to aid in the prediction of extubation readiness, but no single method has been universally accepted, possibly because of the relatively modest specificity and sensitivity of the suggested methods or the complexity of the required methodology (12). Ventilating at very high V_T would cause alveolar damage and volutrauma (13) while weaning and extubating from a very low V_T might cause atelectasis and alveolar collapse which would impact on the outcome of extubation and increase the chance of extubation failure. To our knowledge, no previous study has investigated whether a low V_T contributes to extubation failure.

Our hypothesis was that premature infants that fail extubation are ventilated with lower tidal volumes immediately prior to a trial of extubation compared to those that successfully extubated. Our aims were to compare the tidal volumes in premature infants that successfully extubated compared to premature infants that failed extubation and to explore the ability of V_T to predict successful extubation.

METHODS

Subjects

Infants born at less than 32 completed weeks of gestation without congenital anomalies that were mechanically ventilated at King’s College Hospital (KCH) NHS Foundation Trust, London, UK and St George’s University Hospital (SGUH) NHS Foundation Trust, London, UK between February and September 2018 were eligible for the study. Standard initial respiratory management dictated that infants born at less than 32 weeks of gestation, with an oxygen requirement of >40% and/or signs or respiratory distress were intubated and given surfactant. The infants were ventilated with a size 2.5 or 3.0 mm endotracheal tube on volume-targeted or pressure-controlled, time-cycled ventilation with the SLE6000 neonatal ventilator (SLE, Croydon, UK) or the Stephanie Paediatric Ventilator (Stephan GMBH, Gackenbach, Germany). Local guidelines at both centres did not specify the targeted V_T at extubation but recommended ventilation with a V_T of 5 – 7 ml/kg. The infants were studied when they were clinically stable and ready for extubation. Extubation was considered, if the fraction of inspired oxygen (F_IO_2) was <0.4, the infant had acceptable blood gases (i.e., a pH >7.25 and an arterial pressure of CO_2 [$PaCO_2$] <8.5 kPa), and their breathing rate was above the set ventilator rate. Sedation was discontinued at least 12 hours before extubation and infants were receiving caffeine at a standard maintenance dose. The study was registered as a service evaluation with the Clinical Governance Departments of KCH and SGUH and, as it was not a research study, did not require informed parental consent.

Protocol and respiratory function parameters

When the clinical team decided that an infant was ready for extubation, they were studied prospectively, within four hours before extubation. Only the first extubation attempt was recorded. The following respiratory function parameters were recorded as measured from the ventilator's inbuilt pneumotachograph and proximal pressure sensor: F_IO_2, mean airway pressure (MAP), backup ventilator rate, total respiratory rate, peak inflation pressure (PIP), positive end expiratory pressure (PEEP), inspiratory time and expiratory V_T. The mean value of V_T over a period of 10 minutes was calculated. V_T was also expressed corrected for body weight (V_T/kg). The infants were extubated on to heated, humidified, high-flow nasal cannula or nasal CPAP at the discretion of the clinical team. Reintubation within 72 hours of extubation was the primary outcome of the study (14). Indications for reintubation included respiratory acidosis (pH < 7.25 and $PaCO_2$ > 8.5 kPa), a significant apnoea requiring bag and mask ventilation or frequent episodes of apnoea requiring stimulation, or an F_IO_2 > 0.6 to maintain an oxygen saturation in the range of 91–95% (14).

Information from the medical notes

The following information was collected from the medical notes: gender, gestational age at birth, birth weight, postmenstrual age at extubation, hematocrit at extubation, partial pressure of CO_2 ($PaCO_2$), whether the infants had a patent ductus arteriosus (PDA), had been exposed to antenatal or postnatal steroids or had an IVH. Birth weight z-scores were calculated using British national reference data (15). A PDA was diagnosed clinically and confirmed by echocardiography. Administration of antenatal corticosteroids was recorded as positive if at least two doses were given. Postnatal corticosteroids were considered in mechanically ventilated infants more than seven days of age with an F_IO_2 requirement of more than 50% (16). The cranial ultrasound was recorded as normal if there was no intraventricular haemorrhage greater than germinal matrix haemorrhage or other intracranial pathology.

Sample size

The sample size calculation was based on the observation that prematurely born infants that later developed BPD had a V_T which was 2.6 ml/kg higher than prematurely born infants that did not develop BPD (7). The standard deviation of V_T/kg was shown in one study to be 1.4 ml/kg (17). Fifteen subjects in each group enabled detection of a difference in V_T/kg of 2.6 ml/kg between the two groups with 95% power at the 1% level.

Statistics

Data were tested for normality using the Kolmogorov–Smirnoff test, were found to be non-normally distributed and are thus presented as median/interquartile range.

Differences between infants who failed extubation and those who succeeded extubation were assessed for statistical significance using the Mann-Whitney rank-sum test or the χ^2 test as appropriate. The factors that were statistically different ($p < 0.05$) were inserted into a multivariate binary regression model with success of extubation as the outcome variable. Variables without normal distribution were logarithmically transformed. Multi-collinearity between the independent variables in the regression analysis was assessed by calculation of the tolerance for the independent variables. The performance of V_T in predicting extubation success was assessed by receiver operator characteristic curve analysis and estimation of the corresponding area under the curve (AUC). Statistical analysis was performed using SPSS software (SPSS Inc., Chicago IL).

RESULTS

From 1 February 2018 to 1 September 2018, 93 infants less than 32 weeks of gestation were ventilated at the neonatal unit at KCH and SGUH. Thirty-seven infants were not included due to unavailability of the study team or because they either transferred out or died before extubation. Fifty-six (29 male) infants with a median (IQR) gestational age of 26 (25 - 29) weeks were included in the study. Thirty infants were studied at KCH and 26 were studied at SGUH. Fifty-two infants were ventilated on patient triggered ventilation with volume targeting, two were ventilated on synchronized intermittent mandatory ventilation (SIMV) and two on SIMV with volume targeting. The included infants had a median (IQR) birth weight of 0.84 (0.70 - 1.26) kg. The excluded infants had a median (IQR) gestational age of 26 (24 – 28) weeks and birth weight of 0.90 (0.73 – 1.39) kg, which did not differ significantly compared to those of the included infants ($p=0.390$ and $p=0.101$ respectively). The demographics, antenatal and neonatal characteristics of the included infants are presented in Table 1.

Thirty-six infants (64%) were successfully extubated and the remaining 20 had to be reintubated within 72 hours. The median (IQR) gestational age of the infants that successfully extubated [27 (25 – 30) weeks] was significantly higher compared to the infants that failed extubation [25 (24 – 26) weeks, p=0.002, table 2]. The median (IQR) tidal volume at extubation of the infants that were successfully extubated [7.2 (4.8 – 9.5) ml] was significantly higher compared to the infants that failed extubation [4.3 (4.0 – 5.5) ml, p=0.001, table 2]. The infants that successfully extubated did not differ significantly compared to the infants that failed extubation with regards to birth weight z-score, F_IO_2 at extubation, mean airway pressure at extubation or incidence of PDA (table 2). The incidence of successful extubation was not different between the two participating centres (table 2).

Following binary multivariate regression with success of extubation as the outcome variable, tidal volume was significantly associated with extubation success (adjusted p=0.022, confidence intervals: 1.07 – 2.34), but gestational age was not (adjusted p=0.167, confidence intervals: 0.91 – 1.77). The receiver operator characteristic curve analysis demonstrated that in predicting successful extubation, the V_T had an AUC of 0.786. A V_T higher than 4.5 ml predicted successful extubation with 82% sensitivity and 58% specificity.

DISCUSSION

We have demonstrated that infants that successfully extubated were ventilated with higher tidal volumes before extubation compared to the infants that failed extubation and that the tidal volume predicted the outcome of extubation with moderate sensitivity and specificity.

A number of previous studies have explored which targeted V_T should be used during VTV. Initial settings in preterm infants with respiratory distress syndrome start from a V_T of 4 ml/kg and go as high as 6 ml/kg due to a relatively high dead space of the flow sensor and decreased compliance (18). Infants with established severe BPD might require even higher V_T reflecting the increase in alveolar dead space and the long time constants (17). Furthermore, during weaning of prematurely born ventilated infants, low volume-targeted levels have been shown to increase the work of breathing suggesting that, a volume-targeting level of 6 mL/kg, rather than a lower level, should be used (8, 19). In our study we report values of V_T in the range of 5 – 7 ml/kg which are in keeping with the previously mentioned studies and current recommendations.

In using the pre-extubation V_T to predict the outcome of extubation we report a sensitivity of 82% and a specificity of 58%. The predictive ability of this method is arguably only moderate and certainly not superior to other predictive tools (12). This is not a surprising finding, given that extubation failure has been associated with numerous clinical parameters which could not be assessed by the measurement of V_T alone. Such parameters are the functional integrity of the respiratory muscles (20) and the presence of systemic or respiratory infection (21). We cannot thus advocate that knowledge of the V_T can inform the clinician of the likely outcome of extubation. We can, however, highlight that extubating from low tidal volumes is associated with extubation failure. This information is clinically useful in assisting the physician on selecting the most appropriate ventilation and weaning strategy and deciding on the optimal timing for extubation.

It is interesting that infants who were successfully extubated were ventilated with higher tidal volumes than the infants that failed, while in the same time, other respiratory parameters such as the mean airway pressure, the respiratory rate, the oxygen requirement and the levels of carbon dioxide did not differ between the two groups. This might be a reflection of their underlying respiratory condition, as infants that are in a better respiratory state would achieve higher tidal volumes with the same settings compared to infants that are in a poorer respiratory condition. It is also interesting that although the uncorrected "crude" value of V_T was related to the outcome of extubation, the corrected-for-weight value was not different across the two groups. In the multivariate model that we applied, the gestational age was not retained as an independent predictor of extubation outcome. Although tidal volume and gestational age are not completely independent parameters, these two observations point towards the concept that a certain critical amount of lung parenchyma (V_T) is more important for independent breathing and successful extubation than the relative developmental maturation (GA). We recently reached similar conclusions when assessing the radiographic area in infants with congenital diaphragmatic hernia, where the total crude lung area was more predictive of survival than the weight-adjusted one (22).

Our study has strengths and some limitations. It is the first to investigate a possible relation between the tidal volume during weaning/extubation and the subsequent outcome of extubation. The study was conducted prospectively in two high-volume centres in London in an effort to minimise the impact of local single-unit practice on our results. Furthermore, the measured expiratory tidal volume is a ventilator-derived parameter that is readily available with all currently available neonatal ventilators and can be easily read at the cotside by the attending clinical team. We should acknowledge as a limitation that we didn't collect data on infection in our cohort: it would be plausible that sepsis would impact on the outcome of extubation (23) irrespective of the targeted volume during ventilation. Proven infection though, is an elusive concept since all premature ventilated infants are treated with broad spectrum antibiotics regardless of proven infection as the radiological appearance of respiratory distress syndrome might not be distinguishable from that of congenital pneumonia (24).

In conclusion successful extubation in prematurely born infants is associated with higher tidal volumes compared to in infants who failed extubation. We speculate that a lower V_T prior to exubation may cause atelectasis and lead to extubation failure.

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Conflict of interest: None to declare.

Contributor statement: TD conceived the study, participated in the analysis of the data and drafted the first version of the article. EW and HA collected the data and participated in the analysis of the data, SS contributed to data collection and critically reviewed the manuscript, AH contributed to data collection and critically appraised the manuscript. AG supervised the project, contributed to the interpretation of the results and critically revised the manuscript. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

List of abbreviations:

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
GA	Gestational age
IVH	Intraventricular haemorrhage
MAP	Mean airway pressure
$PaCO_2$	Arterial pressure of carbon dioxide
PDA	Patent ductus arteriosus
PEEP	Positive end expiratory pressure
PIP	Peak inflation pressure
SIMV	Synchronised intermittent mandatory ventilation
V_T	Tidal volume
VTV	Volume targeted ventilation

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Table 1: Characteristics of the study population and ventilation parameters before extubation

Antenatal steroids, n (%)	51 (91)
Gestational age (weeks)	26 (25 – 29)
Birth weight (gr)	835 (700 – 1260)
Birth weight z score	-0.30 (-0.97 – 0.25)
Male sex, n (%)	29 (52)
Surfactant, n (%)	100 (100)
Postmenstrual age at extubation (weeks)	28 (26 – 31)
FiO_2 at extubation	0.23 (0.21 – 0.26)
Mean airway pressure (cmH_2O)	8.2 (7.0 – 10.0)
Backup rate	40 (35 – 50)
Total respiratory rate	59 (52 – 66)
Peak inflation pressure (cmH_2O)	18 (15 – 23)
PEEP (cmH_2O)	5 (4.5 – 5.5)
Inspiratory time	0.37 (0.35 0.40)
Partial arterial pressure of CO_2 (kPa)	5.7 (4.8 – 6.1)
Hematocrit (%)	42 (38 – 47)
Caffeine at extubation, n (%)	53 (95)
PDA at extubation, n (%)	16 (29)
Postnatal steroids pre extubation, n (%)	3 (5)
Normal cranial ultrasound, n (%)	28 (50)

Values are presented as median (IQR) or number (percentage)

Table 2: Comparison of the characteristics of the infants that successfully extubated versus the ones that failed extubation

	Successful extubation N=36	Failed extubation N=20	P value
Gestational age (weeks)	27 (25 – 30)	25 (24 – 26)	**0.002**
Postmenstrual age at extubation (weeks)	29 (26 – 32)	26 (25 – 28)	**<0.001**
Birth weight (gr)	900 (730 – 1475)	740 (675 – 910)	**0.018**
Birth weight z-score	-0.28 (-0.98 – 0.49)	-0.47 (-0.98 – 0.10)	0.388
Day of life at extubation	4 (1 – 8)	4 (1 – 7)	0.820
FiO_2 at extubation	0.22 (0.21 – 0.25)	0.25 (0.21 – 0.30)	0.053
Mean airway pressure (cmH_2O)	7.7 (7.0 – 9.8)	8.6 (7.1 – 10.0)	0.456
Total respiratory rate	60 (53 – 67)	58 (50 – 64)	0.297
$PaCO_2$ (kPa)	5.72 (4.36 – 6.10)	5.70 (5.24 – 5.96)	0.993
PDA	9 (56)	7 (44)	0.242
Normal cranial US	21 (75)	7 (35)	0.094
King's College Hospital	19 (63)	11 (37)	0.873
Tidal volume (ml)	7.2 (4.8 – 9.5)	4.3 (4.0 – 5.5)	**0.001**
Tidal volume (ml/kg)	5.9 (5.0 – 7.4)	5.8 (5.6 – 6.4)	0.643

Values are presented as median (IQR) or number (percentage)